

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 10 APR 2006
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Applicant's or agent's file reference 15922-3PCT	<div style="display: flex; justify-content: space-between;"> FOR FURTHER ACTION See Form PCT/IPEA/416 </div>	
International application No. PCT/CA2004/002070	International filing date (<i>day/month/year</i>) 02 December 2004 (02-12-2004)	Priority date (<i>day/month/year</i>) 05 December 2003 (05-12-2003)
International Patent Classification (IPC) or national classification and IPC IPC: A61K 41/00 (2006.01), A61P 37/02 (2006.01), A61N 5/06 (2006.01), A61K 39/00 (2006.01), A61K 35/14 (2006.01), A61K 35/12 (2006.01)		
Applicant UNIVERSITE DE MONTREAL ET AL		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u> 2 </u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input checked="" type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of <u> 32 </u> sheets, as follows: <input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box. b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions). 4. This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application		
Date of submission of the demand 05 October 2005 (05-10-2005)	Date of completion of this report 5 April 2006 (05-04-2006)	
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Ryan Jaecques (819) 953-6570	

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/002070**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on:
- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rules 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
- ☐ the international application as originally filed/furnished
- ☒ the description:
- ☒ pages 1, 3-15 and 17-21 as originally filed/furnished
- ☒ pages* 2 and 16 received by this Authority on 05 December 2005
- ☐ pages* received by this Authority on _____
- ☒ the claims:
- ☐ pages as originally filed/furnished
- ☐ pages* as amended (together with any statement) under Article 19
- ☒ pages* 22-51 received by this Authority on 05 December 2005
- ☐ pages* received by this Authority on _____
- ☒ the drawings:
- ☒ pages 1-4 as originally filed/furnished
- ☐ pages* received by this Authority on _____
- ☐ pages* received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-12, 14-17, 32-43 and 45-49

because:

☒ the said international application, or the said claims Nos. 1-12, 14-17, 32-43 and 45-49

relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject-matter of claims 1-12, 14-17, 32-43 and 45-49 relates to methods of medical treatment of the human or animal body according to Rule 67.1 PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exists in the PCT. The patentability can also be dependent upon the formulation of the claims. Certain national offices do accept claims worded as method of medical treatment while others rather accept claims worded as use claims and would then recognize the industrial applicability of these claims. Under the PCT Rules, no industrial applicability can be acknowledged. With regard to the above-cited claims, it should be noted that Rule 67.1 PCT is relevant insofar as independent claims 1 and 32 may define a use, but also include the treatment of cells which may be effected *in vivo*, making them the equivalent of medical methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/002070**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Claims	<u>6-8, 17, 26-31, 37-39, 48 and 49</u>	YES
	Claims	<u>1-5, 9-16, 18-25, 32-36 and 40-47</u>	NO
Inventive step (IS)	Claims	<u>6-8, 26-28 and 37-39</u>	YES
	Claims	<u>1-5, 9-25, 29-36 and 40-49</u>	NO
Industrial applicability (IA)	Claims	<u>13, 18 and 44</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)**Prior Art Cited:**

- D1:** WO 02/079183
D2: WO 01/24824
D3: WO 96/07431
D4: US 5,773,460
D5: Guimond, M et al., *Blood*, 100(2) (15 July 2002), pp. 375-382
D6: Chen, B. J. et al., *Blood*, 99(9) (1 May 2002), pp. 3083-3088
D7: Brasseur, N. et al., *Photochem. Photobiol.*, 72(6) (2000), pp. 780-787

Summary of the Invention:

The present invention relates to the use of photodynamic therapy (PDT) in the treatment of immunologic disorders, infections and cancers. Central to the invention is the exposure of photoactivatable rhodamine derivatives to a sample of cells, which can later be reintroduced into the body. Cells that are activated tend to localize these compounds more so than resting cells, resulting in the destruction of these cells once exposed to an activating (visible) light source, since the activated form of these compounds is very cytotoxic. The compounds are also known to have a low potential for DNA damage, mutation and/or carcinogenesis associated with their use. Cells that may be subject to this PDT include immune cells, infected cells and cancer cells. Destruction of the activated cells results in a release of antigen which is able to act as a vaccine upon reintroduction to the patient and initiates an immune response which, in turn, can effect the prophylaxis and/or treatment of immunologic disorders, infection and cancers.

Summary of the Cited Art:

D1 discloses the production of rhodamine derivatives (including TH9402) that function as photosensitizers, and which preferentially localize in immunoreactive cells, where these cells can be subsequently destroyed by exposing them to visible light (PDT). The treatment may be in conjunction with an acceptable pharmaceutical carrier for the *ex vivo* elimination of reactive immune cells in patients with immunologic disorders. These rhodamines were found to be effective in preventing graft-versus-host disease (GVHD), and in the treatment of infections caused by Gram⁺ and/or Gram⁻ bacteria, viral infections, leukemias, multiple myelomas and lymphomas, and solid tumours.

D2 discloses photoactivatable pharmaceutical compositions for the selective destruction of immunoreactive cells by using PDT in conjunction with a rhodamine derivative as photosensitizer (including TH9402). This was accomplished *ex vivo* for the treatment of immunologic disorders, GVHD and organ rejection.

(Continued in Supplemental Box)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 22 and 32 do not comply with Article 6 PCT. There is no apparent difference between preventing a disease and being protected from it, nor is there anything in the description to make this distinction. Clarification of the terms should thus be made.

Claims 13 and 44 are still unclear and thus do not comply with Article 6 PCT, despite the explanation forwarded by the applicant in response to the Written Opinion of the ISA. Specifically, the method the applicant describes in his response to the Written Opinion describes a means by which the treatment is performed. This is not the issue. What is unclear is the use of "perfusion" in the claims, since that term is generally defined as the passage of fluid through a tissue or organ, or the bathing of an organ with said fluid. Claim 13, for example, would then define the use of claim 12, wherein the treatment is *ex vivo* and is effected by passing fluid (blood) through a tissue or organ. This does not appear to make sense. The treatment is said to be done outside the body (*ex vivo*) but the organ is inside the body and apparently requires the use of the PDT. Since the treatment is not done by passing the fluid through the tissue or organ, but rather by a PDT machine, followed by reinfusion of said fluid into the patient, the claim is considered misleading and should be reworded to more clearly define the subject-matter for which protection is sought.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D3 discloses the synthesis of photosensitive rhodamine derivatives that are useful in PDT. Also disclosed is the preferential localization of these compounds in malignant cells, and their use in the treatment of tumours and in bone marrow purging for autologous transplantation.

D4 discloses photoactivatable rhodamine derivatives, including some of those encompassed by the present claims, for use in PDT. These derivatives were found to be preferentially localized in malignant cells, leading to the selective destruction of these cells and the *in vitro* treatment of tumours via the purging of cancerous clones in the bone marrow of chronic myelogenous leukemia (CML) patients.

D5 discloses that PDT of TH9402-exposed T-cells led to the selective elimination of immunoreactive T-cell populations, and determined that this can be applied to the treatment of GVHD and other alloimmune and autoimmune disorders.

D6 discloses that mice injected with irradiated allogeneic spleen cells previously treated with TH9402 and exposed to visible light at 514 nm (photodynamic cell purging or PDP) allowed 90% of the recipients to remain tumour-free and free of GVHD for a 100 day observation period, and yet graft-versus-leukemia (GVL) activity is not impaired.

D7 discloses the use of the photosensitizer TH9402 and visible light in the PDT-mediated selective elimination of CML and breast cancer cells.

Novelty:

Claims 1-5, 9-16, 18-25, 32-36 and 40-47 are objected under Article 33(2) PCT as being anticipated by one or more of **D1** to **D7**. The relevant claims and reasoning for the objections are discussed below.

In his letter referring to the first Written Opinion, the applicant argued the relevance of the prior art cited in regard to the novelty of the present claims, indicating that there are distinct differences between the treatments as presently taught, and those of the art.

There are three independent claims on file: claims 1, 18 and 32. Claim 1 is directed to the preparation of a medicament for the prevention, protection or treatment of an immunological disorder, infection and/or a cancer in an individual; claim 18 is directed to an immunologic vaccine; and claim 32 to a method for preparing an immunologic medicament for the prevention, protection from or treatment of an immunological disorder, infection and/or a cancer in an individual; all of said independent claims requiring the PDT-treatment of cells with one of the defined rhodamine derivatives.

In his dismissal of the prior art, the applicant raised a few issues that will be dealt with in turn. First, it was pointed out that claim 1 is directed to a new use of a medicament. It appears that the applicant is suggesting that this distinguishes the subject-matter of this claim from the art, which teach the use of PDT-treated cells for the treatment of identical diseases (*vide infra*). Claim 1 is in Swiss-claim format, but the underlying subject-matter is the use of PDT-treated cells for the stated purposes. It referring to a "medicament" does not make the claim novel over disclosures teaching the same use, but without directly using the term, nor is it clear how it is supposed to.

The second issue raised by the applicant is that the prior art treatment involved the use of chemotherapy and radiation in association with the PDT-treatment of the grafts, which is not required by the invention of the present application.

It is noted, however, that none of the present claims preclude the concomitant or sequential use of chemotherapy or radiation therapy, when used with grafts or otherwise. A vaccine can be broadly defined as a preparation containing whole or parts of disease-causing organisms used to induce immunity to said disease; an "immunologic medicament" can be exemplified by a vaccine, and is thus broader in scope. There is nothing in this definition that would distinguish the claimed invention over the prior art if the differences are merely in the use of the PDT-treated cells, as these claims do not exclude this possibility from their scope.

(Continued in Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Supplemental Box

For example, claim 1 is essentially directed to the use of cells PDT-treated with a particular rhodamine derivative for the above-mentioned purposes. The other steps that are occurring during the actual medical administration of the medicament are irrelevant as the claim broadly encompasses the use of such treated cells in those capacities. It is not clear how the art does not apply simply because additional steps may be present when, or before, the PDT-treated cells are reintroduced into the patient. Similarly, it is irrelevant *why* the patient is being administered with the PDT-treated cells, since "immunologic medicament" appears to encompass the use of these cells in *any* immunologic capacity. Therefore, this cannot be used to render the prior art irrelevant. It is also worth mentioning that on page 31 and 32 of **D1**, the use of PDT in the treatment of cancers is outlined: the additional use of chemotherapy and radiation therapy is preferred, but is not required.

It is further noted that although claim 18 is directed to a vaccine *per se*, claims 1 and 32 specifically refer to the use of PDT-treated cells for the treatment of the stated conditions. The treatment of these conditions extends beyond the common definition of vaccine and thus encompasses merely using these cells in some form in a treatment for certain conditions; it does not require that there be any future immunity afforded. Therefore, it is clear that even if the prior art merely mentions the use of cells PDT-treated using identical rhodamine derivatives in the treatment of the same conditions, that it will fall within the scope of these claims.

The applicant also raises the argument that the prior art only teaches one administration step, whereas the present invention is taught to be able to be administered multiple times. It is unclear how this is relevant. The claims do not require this, nor is it anything more than a preferred embodiment. The prior art does not teach that multiple administrations cannot be done, but suggests that multiple administrations *need* not be done to achieve the desired result.

Another of the applicant's rebuttals that is used to base many of his arguments was that it is common practice to wash the PDT-treated cells, removing the dead cells and debris from the sample prior to reintroduction. This would effectively remove the material responsible for the result obtained from the present invention. It is noted that there was nothing found to support this position in any of **D1** to **D7**. It is clear from the examples of **D1**, for example, that the only washing that is done is after infusing the cells with the rhodamine derivatives. There is no mention of washing after PDT-treatment, nor the removal of any material. The applicant argues that this is what is done in the art but, although the washing step after the *dyeing* is explicitly mentioned, there is conspicuously no mention of the lavage step the applicant refers to. It is thus clear that the dead cells, debris etc. are still present in the sample, and are therefore reintroduced with the living cells. There is also nothing in these documents that would indicate that such a step is done or would be desirable. While it may be common practice in certain circumstances, it is clear that such a washing step was not present in **D1** to **D7**, making these documents prejudicial to the novelty of claim 1. Claim 32 is also anticipated as the method is identical to those used in the art for such treatments (or medicament preparations).

It is acknowledged that the concept of a vaccine is unique to the present invention, with the exception of **D1**. Therefore, claim 2 is only deemed anticipated by this art. However, this is based on "vaccine" referring to the prevention of disease only. If the term is extended to include treatment, then all of **D1** to **D7** apply, since they all teach the reinfusion of the cells, dead or otherwise, after PDT, making them the equivalent of a vaccine for the treatment of the disclosed diseases.

In respect of claims 3, 4 and 33-35, the applicant argues that the reinfused cells of the art excluded the immunoreactive T cells, to only include resting cells. Again it is argued that the "customary lavages" would result in the relevant materials being removed making the medicaments different than those of the present invention. There is no evidence to support that this lavage step was actually done in **D1**, **D2**, **D5** or **D6**, however, so this argument is moot.

The objections to these claims as well as 5 and 36 are thus also maintained.

The novelty objection to claims 6, 7, 37 and 38 has been withdrawn, as it is noted that **D1** uses the rhodamine derivatives as a means for treating bacterial or viral infections, and not the PDT-treated *cells* themselves as required by the present claims.

Since there does not appear to be support for the applicant's assertion that there is a lavage step in the art that would change the composition of the medicament in relation to that of claims 9-11 and 40-42, the objection against these claims is maintained (see **D1**, **D3**, **D4** and **D7**).

(Continued in Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Supplemental Box

Claims 12-16 and 43-47 were argued to be novel because the use of the rhodamine derivatives is new. Since the applicant's arguments regarding the novelty of the use are not convincing for the reasons already mentioned, these claims are still deemed anticipated by **D1** to **D7**.

With respect to claims 18-25: there is no support for the contention that the dead cells and fragments are indeed removed from the PDT-treated aliquots. These components would still be present upon reinfusion into the patient, and would thus act as a vaccine. In fact, it is noted that the treatment of immunologic diseases such as GvHD (graft versus host disease) and autoimmune diseases on pages 33 and 34 of **D1** are suggestive of vaccination without using this term explicitly. In order to prevent GvHD, for example, the inventors indicate that the patient and donor's cells are mixed until an immune reaction occurs. The PDT is then performed and the cells reintroduced into the patient. The PDT destroys the activated cells, releasing cellular components of the dead cells into the mixture. When this is reintroduced into the patient, it will have a vaccination effect and prevent an immune response when the graft is performed (i.e. prevent GvHD). A similar protocol is described for autoimmune reaction prevention. It is thus clear that, at least in regard to immunologic diseases, that **D1** teaches the use of PDT-treated cells as vaccines. Claims 26 and 29-31 were dropped from this objection because it is acknowledged that **D1** does not teach the use of such treated cells in the manufacture of a vaccine (see definition proviso above) for preventing cancers or infections.

It is acknowledged that the application does contain patentable subject-matter: for example, if the reference to treatment were excluded from the claims, then vaccination against cancers and infections would be considered novel, as none of the cited art teaches these uses. In relation to the others, however, the features to which the applicant refers in attempting to establish novelty are currently not present in the claims, and thus cannot be used to distinguish the invention over the prior art. Features which do not form part of the claims cannot be drawn upon to establish novelty, as the scope of the claims encompass much broader subject-matter (including the prior art) in their absence. For instance, the present claims do not require specific cells to be used or that the PDT-treated cells are only intended for use when no other chemotherapy or radiotherapy is being administered, and therefore cannot be relied upon to establish the novelty of the claims.

Presently, novelty can be acknowledged for the subject-matter of claims 6-8, 17, 26-31, 37-39, 48 and 49.

Inventive Step:

Claims 1-5, 9-16, 18-25, 32-36 and 40-47 are considered to lack an inventive step under Article 33(3) PCT in light of the fact that they were found to be anticipated by the art.

Claims 17-25, 29-31, 48 and 49 are also considered un inventive in light of the art. The applicant argued all the objections under this Article; however, his reasons were not persuasive in some cases.

The objection to a lack of inventive step for claims 8, 28 and 39 are withdrawn, as it is acknowledged that the art does not teach, nor suggest, the use of PDT-treated cells themselves for the prevention, or treatment of infections.

Claims 17 and 48 were objected to as lacking an inventive step over the art, especially **D1** to **D4**. The applicant agreed with the examiner's assessment that using antigen-presenting cells in conjunction with immunising antigens is known. The only argument against the objection relies on the alleged washing step that would remove the material responsible for the result. Since no evidence of such a washing step was found in the art, this objection is maintained.

The applicant also argued the objections made to claims 18-22, averring that the carriers in **D2** to **D4** are oriented toward stabilisers, whereas those of the present application are directed to a substance that would promote the immunisation process, and that they are therefore non-obvious variants. The examiner notes, however, that the term "carrier" is simply a vehicle for the active ingredient, as the term is used in the art. Although the applicant may prefer to use compounds/materials which promote immunisation, the use of "carrier" in these claims is much broader than this interpretation. Presently, and as would be understood by a person skilled in the art, the term encompasses physiologically tolerated vehicles (solvents etc.) The scope of the term is thus much broader than the interpretation given by the applicant. It is further noted that carriers are well known

(Continued in Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Supplemental Box

in the art, simply adding one to an active agent is not considered inventive unless some unexpected technical benefit is derived from doing so. The objection is therefore maintained.

In light of the above arguments, the objections to claims 23-25 and 29-31 are similarly not maintained.

Newly-submitted claim 49 is also deemed un inventive in light of D1 to D7. Although there may be no explicit mention in the art of the procedure of PDT-treated cell administration being repeated, a person skilled in the art would know to do so if deemed appropriate.

In their present form, an inventive step *can* be acknowledged for claims 6-8, 26-28 and 37-39.

Industrial Applicability:

Claims 13, 18 and 44 comply with Article 33(4) PCT as being generally related to the use of cells PDT-treated, *ex vivo*, for the protection from and prevention and treatment of various diseases and conditions, as well as to immunologic vaccines comprising such treated cells, which is deemed to be industrially useful subject-matter.

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to present their own antigens to professional antigen presenting cells, such as dendritic cells. Such antigen presentation can lead to the development of a response of the immune system toward these immunizing antigens. Many reports have demonstrated the usefulness of adjuvants to boost the immune response toward the killed cells. Among others, pertinent references such as works by Korbelyik (Korbelyik *et al*, *Laser Med. Surg*, 14 (1996), 329-334, *Can. Res.*, 56, (1996) 5647-5565; Chen *et al*, *SPLE*, 394 (2000), 26-32), as well as Nordquist *et al* (International Patent Applications published under Nos. WO 96/31237 and WO 99/47162A1) have demonstrated the usefulness of such an approach. Moreover, the usage of oxygenated species in blood components has been described previously using ozone as the chemical agent in conjunction with irradiation (Zee *et al*, US Patent No. 4,632,980; Fish *et al*, US Patent No. 4,831,268, Mueller *et al*, US Patent No. 4,968,483). Photodynamic Therapy has also been extensively described in "*Photosensitizing Compounds: their Chemistry, Biology and Clinical uses*" (1989, John Wiley & Sons, Chichester, UK, ISBN 0471923087). Many other pertaining references relating to the usage of Photosensitizers in the treatment of tumor masses combined with antibodies (Levy *et al*, US Patents Nos. 5,095,030 & 5,283,225) as well as ligands and antibodies (Pendry *et al*, US Patent No. 5,241,036). Autoimmune vaccines have been described by Bolton, A.E. (US Patent No. 6,204,058B1) (International Patent Application published under No. WO 98/07436) on which Rheumatoid Arthritis is treated using leukocytes with increased expression of specific antigens by oxidizing agents, UV irradiation and high temperature.

Extracorporeal Photopheresis has been described as a successful therapy for the treatment of Hepatitis C, in combination with other means such as Interferon alpha (O'Brien, C.B. International Patent Application published under No. WO 97/37654; McLaughlin S.N. *et al*, International Patent Application published under No. WO 97/36634), as well as in the treatment of other illnesses mediated by undesired activated immune cells (McLaughlin *et al*, US Patent No. 5,984,887 and Bisaccia *et al*, US Patent No. 5,426,116). Other studies have been reported regarding the usage of extracorporeal Photopheresis in indications such as organ

AMENDED SHEET

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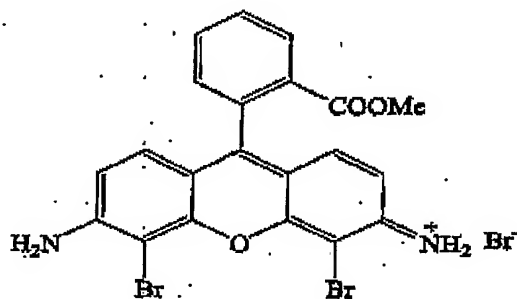
necrosis. Since mainly activated cells will be eradicated by photoactivatable molecules of the present invention (TH9402 and derivatives thereof), analysis of the cell population undergoing apoptosis and necrosis has been evaluated. Data indicates that B-cells, dendritic cells and activated T-cells among others, are rapidly eliminated. This advantage is exploited by inducing the immune system to produce an immune response against autoreactive T-cells. This property has been used in mice models and humans developing GvHD. Peripheral blood cells from individuals with GvHD are harvested, usually by leukopheresis, and exposed to PDT. These treated cells are then reinfused into the individual and this procedure is repeated at regular intervals. This treatment leads to improvement of GvHD that occurs after stem cell transplantation. PDT using photoactivatable molecules of the present invention (TH9402 and derivatives thereof) is able to prevent the development or treat GvHD in mice that received PDT-treated cells at regular intervals. This leads to improved survival of mice infused with PDT-treated cells. In contrast, mice receiving either non-PDT treated cells or media alone are developing GvHD leading to death. This is also shown in Figs. 1A and 1B using Kaplan-Meier survival analysis.

The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

- 22 -

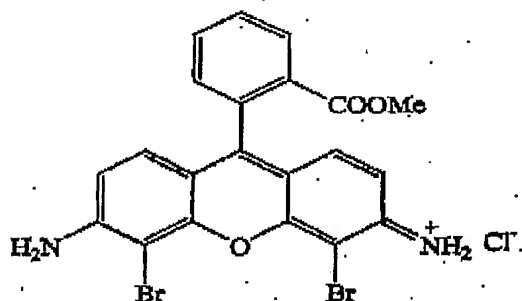
WHAT IS CLAIMED IS:

1. The use of PDT-treated cells (whole or fragments thereof) and/or supernatant thereof in the preparation of an immunologic medicament for use in the prevention, protection or treatment of an immunological disorder, infection and/or a cancer in an individual, which comprises treatment of said cells or components thereof with a photoactivatable molecule selected from the group consisting of:



I

4,5-dibromorhodamine 123 hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrobromide) also called TH9402,



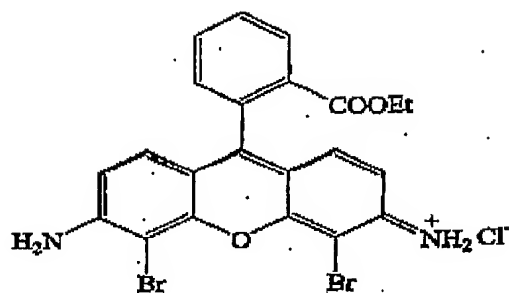
II

4,5-dibromorhodamine 123 hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride),

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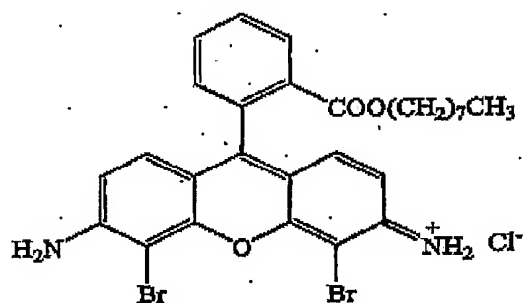
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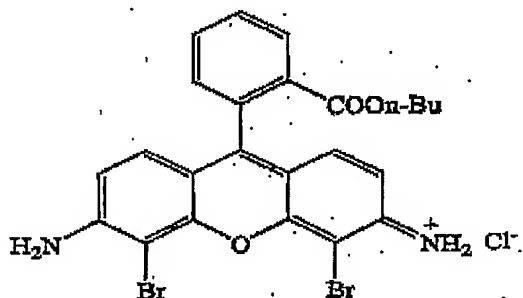
III

4,5-dibromorhodamine 110 ethyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrochloride),



IV

4,5-dibromorhodamine 110 octyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid octyl ester hydrochloride),



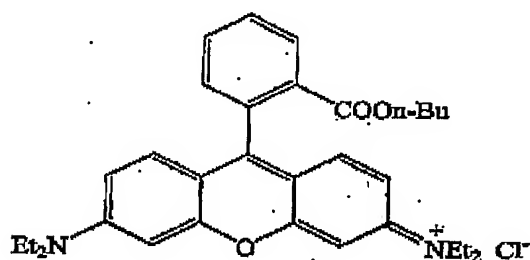
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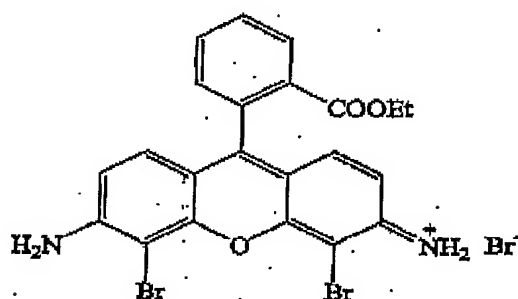
- 24 -

4,5-dibromorhodamine 110 n-butyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrochloride),



VI

rhodamine B n-butyl ester hydrochloride (2'-(6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrochloride),



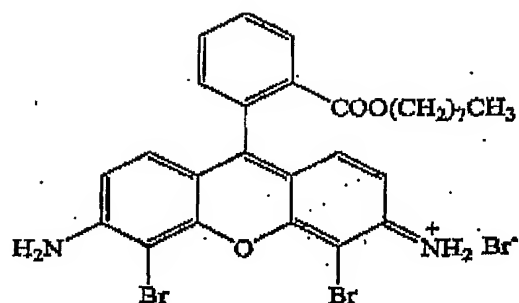
VII

4,5-dibromorhodamine 110 ethyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrobromide),

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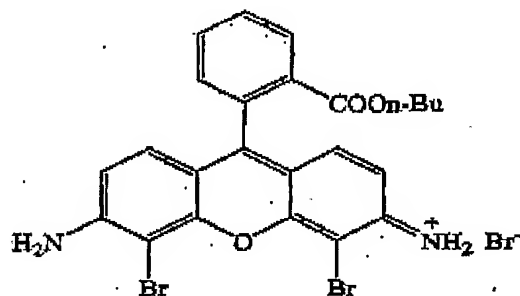
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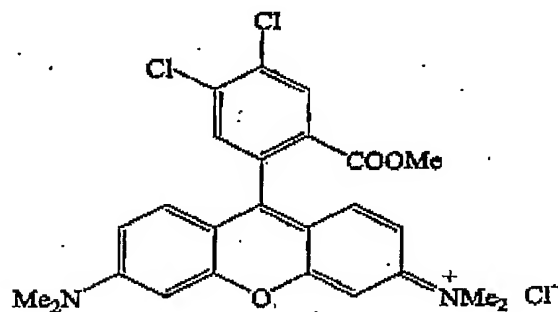
VIII

4,5-dibromorhodamine 110 octyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid octyl ester hydrobromide),



IX

4,5-dibromorhodamine 110 n-butyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrobromide),



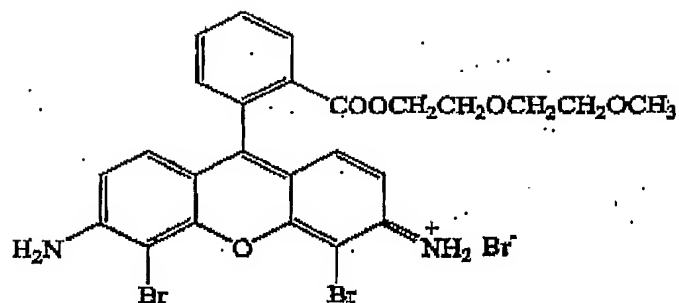
X

4',5'-dichlorotetramethylrhodamine (2'-(6-dimethylamino-3-dimethylimino-3H-xanthen-9-yl)-4',5'-dichloro benzoic acid methyl ester hydrochloride),

AMENDED SHEET

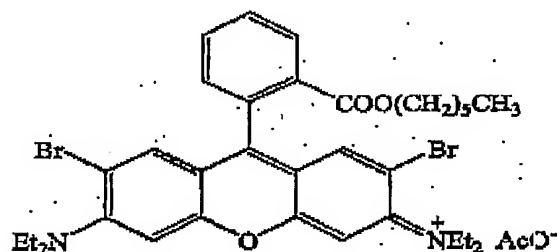
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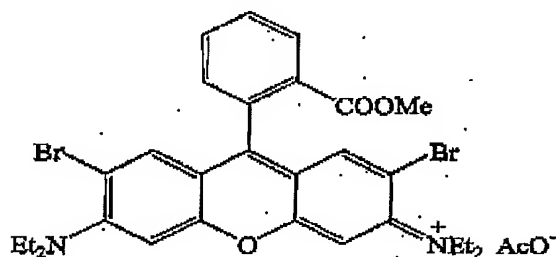
XI

4,5-dibromorhodamine 110 2-(2-methoxy ethoxy)ethyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid 2-(2-methoxy ethoxy) ethyl ester hydrobromide),



XII

2,7-dibromorhodamine B hexyl ester acetate (2'-(2,7-dibromo-6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid hexyl ester acetate),



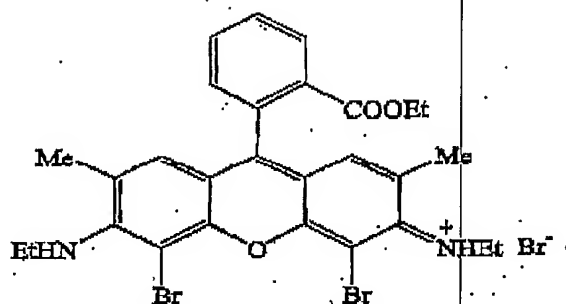
XIII

2,7-dibromorhodamine B methyl ester acetate (2'-(2,7-dibromo-6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid methyl ester acetate),

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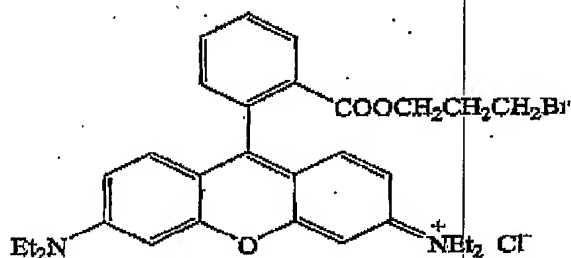
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XIV

4,5-dibromorhodamine 6G hydrobromide (2'-(4,5-dibromo-2,7-dimethyl-6-ethylamino-3-ethylimino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrobromide),



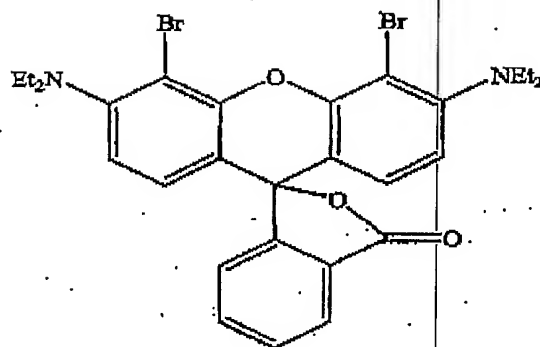
XV

rhodamine B 3-bromopropylester hydrochloride (2'-(6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid 3-bromopropyl ester hydrochloride),

AMENDED SHEET

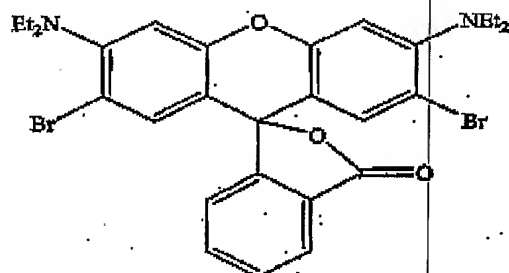
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XVI

4,5-dibromorhodamine B base (3,3-(4',5'-dibromo-3'-diethyl amino-6'-diethyl aminoxanthen-9'-yl)-3H-isobenzofuran-1-one),

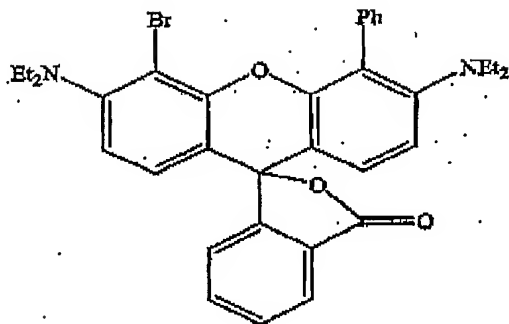


XVII

2,7-dibromorhodamine B base (3,3-(2',7'-dibromo-3'-diethyl amino-6'-diethyl aminoxanthen-9'-yl)-3H-isobenzofuran-1-one), and

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XVIII

4-bromo-7-phenyl-rhodamine B base (3,3-(4'-bromo-3'-diethyl amino-6'-diethyl amino-5'-phenyl xanthen-9'-yl)-3H-isobenzofuran-1-one),

and wherein said photoactivatable molecule is activated by a light of appropriate wavelength, thereby activating said photoactivatable molecule and causing prevention, protection or treatment of said immunological disorder, infection and/or a cancer.

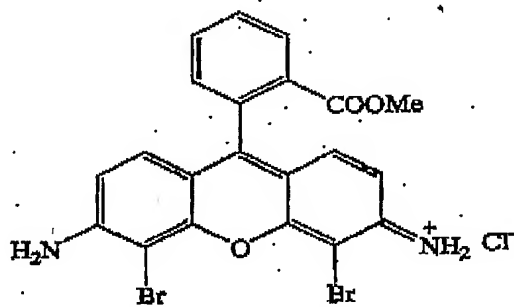
2. The use of claim 1, wherein said immunologic medicament is a vaccine.
3. The use of claim 1 or 2, wherein said immunological disorder is an alloimmune disorder or an autoimmune disorder.
4. The use of claim 3, wherein said alloimmune disorder is Graft-versus-Host Disease or an organ rejection.
5. The use of claim 3, wherein said autoimmune disease is selected from the group consisting of Rheumatoid Arthritis, Multiple Sclerosis, Scleroderma, Lupus, Autoimmune Hemolytic Anemia, Diabetes Mellitus, Progressive Systemic Sclerosis, Idiopathic Thrombocytopenic Purpura, Psoriasis, Ulcerative Colitis and Crohn's Disease.
6. The use of any one of claims 1 to 5, wherein said infection is caused by a bacteria, a virus, a parasite, a fungus, a prion or a protozoan.

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4,5-dibromorhodamine 123 hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrobromide) also called TH9402, and



4,5-dibromorhodamine 123 hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride).

15. The use of any one of claims 1 to 14, wherein said wavelength is in the range of about 400 to about 800 nm.

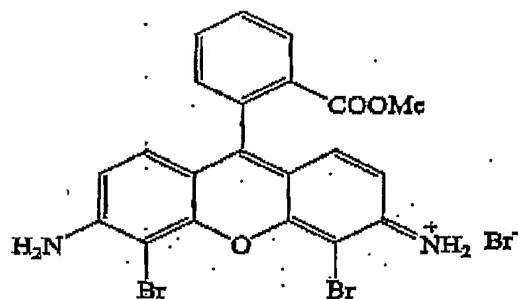
16. The use of claim 15, wherein said wavelength is in the range of about 450 to about 600 nm.

17. The use of any one of claims 1 to 16, which further comprises adding antigen presenting cells selected from the group consisting of dendritic cells, Langerhans cells and growth factors.

18. An immunologic vaccine comprising PDT-treated cells (whole or fragments thereof) and/or supernatant thereof, wherein said cells are treated with a photoactivatable molecule selected from the group consisting of:

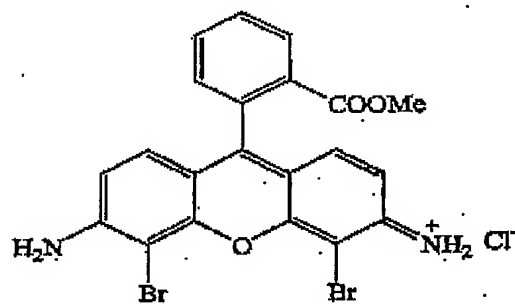
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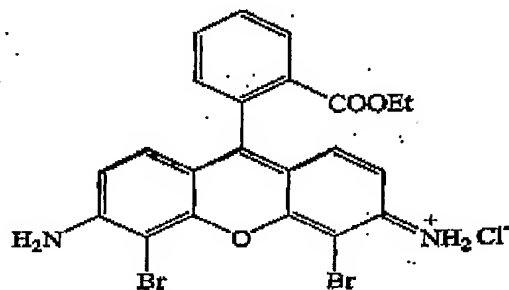
I

4,5-dibromorhodamine 123 hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrobromide) also called TH9402,



II

4,5-dibromorhodamine 123 hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride),



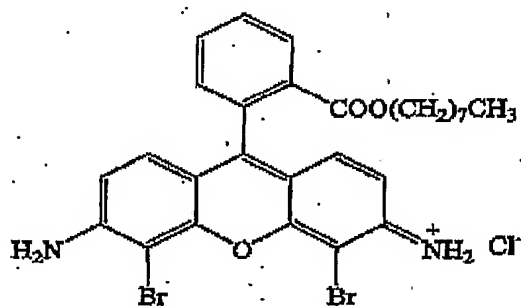
III

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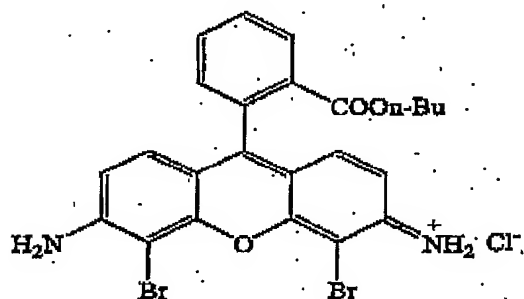
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4,5-dibromorhodamine 110 ethyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrochloride),



IV

4,5-dibromorhodamine 110 octyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid octyl ester hydrochloride),



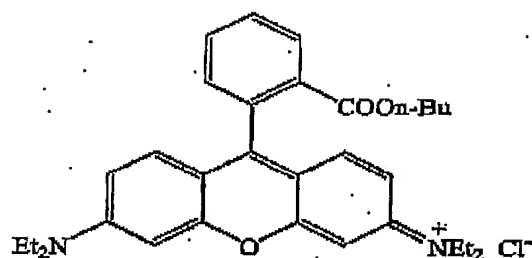
V

4,5-dibromorhodamine 110 n-butyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrochloride),

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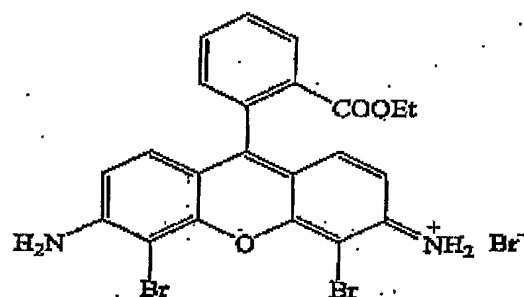
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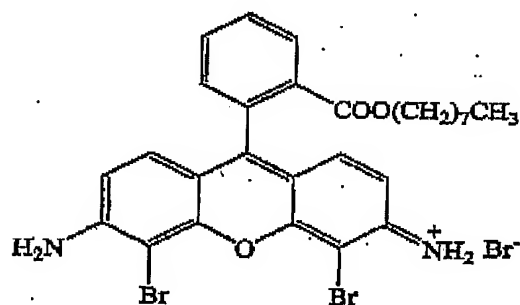
VI

rhodamine B n-butyl ester hydrochloride (2'-(6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrochloride),



VII

4,5-dibromorhodamine 110 ethyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrobromide),



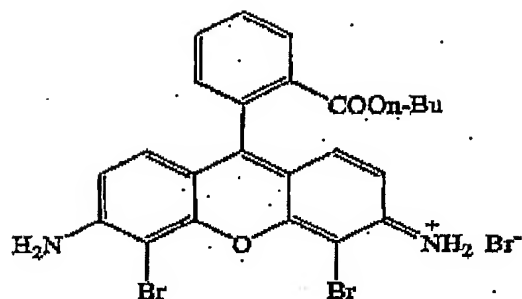
VIII

4,5-dibromorhodamine 110 octyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid octyl ester hydrobromide),

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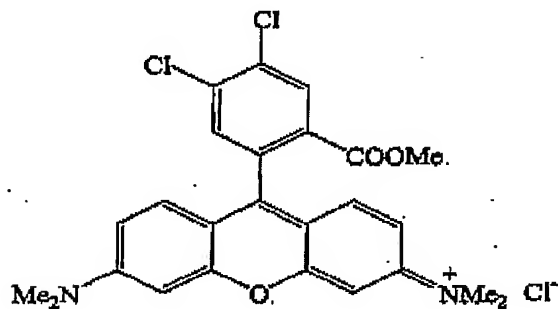
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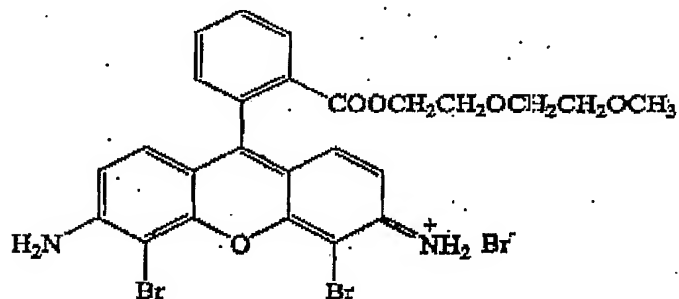
IX

4,5-dibromorhodamine 110 n-butyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrobromide),



X

4',5'-dichlorotetramethylrhodamine (2'-(6-dimethylamino-3-dimethylimino-3H-xanthen-9-yl)-4',5'-dichloro benzoic acid methyl ester hydrochloride),

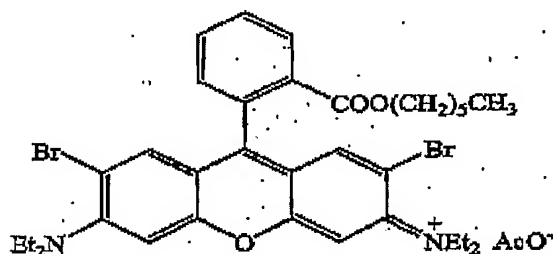


XI

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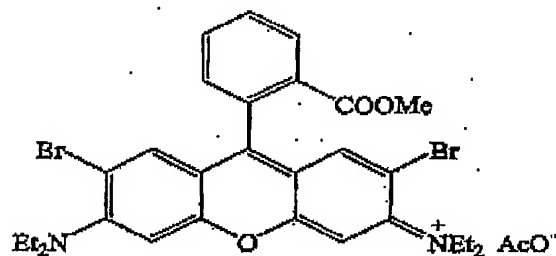
- 36 -

4,5-dibromorhodamine 110 2-(2-methoxy ethoxy)ethyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid 2-(2-methoxy ethoxy) ethyl ester hydrobromide),



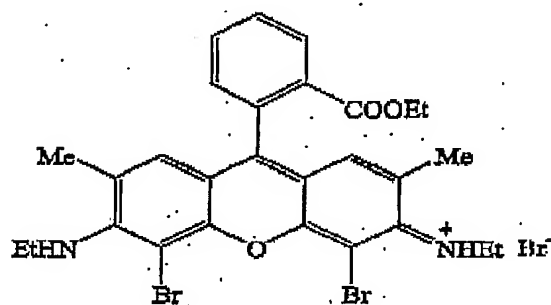
XII

2,7-dibromorhodamine B hexyl ester acetate (2'-(2,7-dibromo-6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid hexyl ester acetate),



XIII

2,7-dibromorhodamine B methyl ester acetate (2'-(2,7-dibromo-6-diethyl amino-3-diethyl imino-3H-xanthen 9-yl)benzoic acid methyl ester acetate),

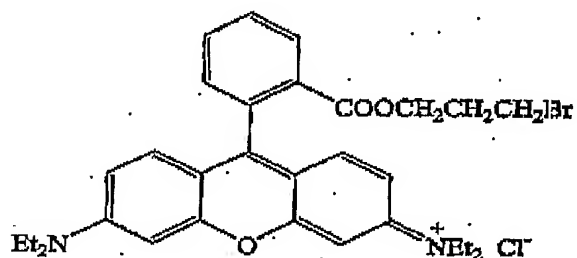


XIV

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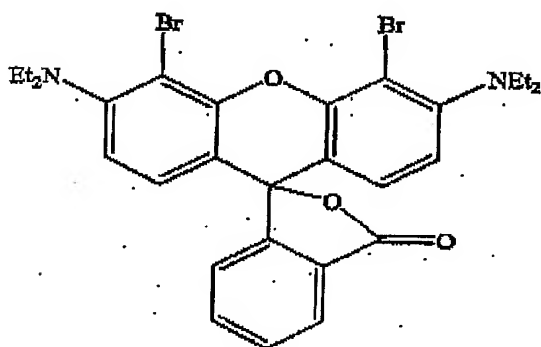
- 37 -

4,5-dibromorhodamine 6G hydrobromide (2'-(4,5-dibromo-2,7-dimethyl-6-ethylamino-3-ethylimino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrobromide),



XV

rhodamine B 3-bromopropylester hydrochloride (2'-(6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid 3-bromopropyl ester hydrochloride),

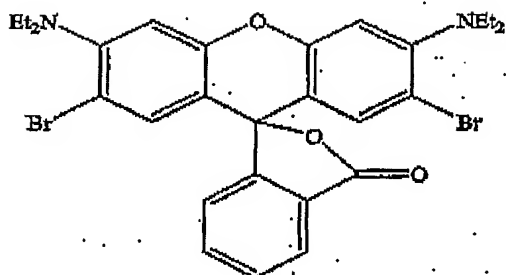


XVI

4,5-dibromorhodamine B base (3,3'-(4',5'-dibromo-3'-diethyl amino-6'-diethyl aminoxanthen-9'-yl)-3H-isobenzofuran-1-one),

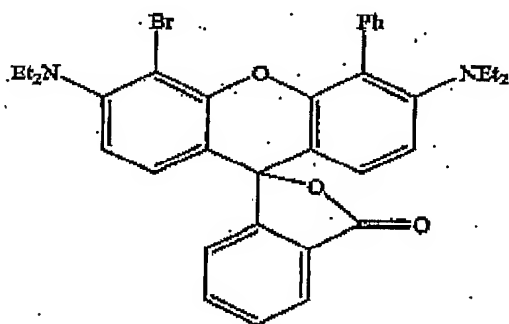
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XVII

2,7-dibromorhodamine B base (3,3-(2',7'-dibromo-3'-diethyl amino-6'-diethyl aminoxanthen-9'-yl)-3H-isobenzofuran-1-one), and



XVIII

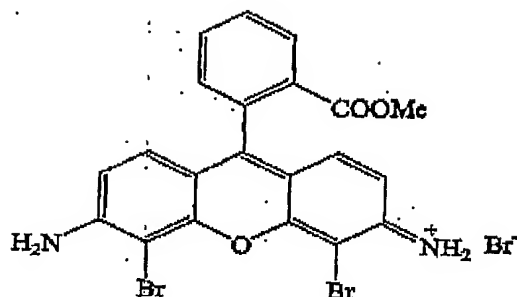
4-bromo-7-phenyl-rhodamine B base (3,3-(4'-bromo-3'-diethyl amino-6'-diethyl amino-5'-phenyl xanthen-9'-yl)-3H-isobenzofuran-1-one).

in association with a pharmaceutically acceptable carrier.

19. The vaccine of claim 18, wherein said photoactivatable molecule is selected from the group consisting of

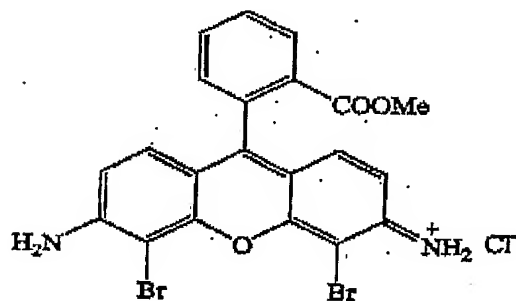
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I

4,5-dibromorhodamine 123 hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrobromide) also called TH9402, and



II

4,5-dibromorhodamine 123 hydrochloride. (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride).

20. The vaccine of claim 18 or 19, wherein said molecule is activatable by a light having a wavelength in the range of about 400 to about 800 nm.
21. The vaccine of claim 20, wherein said wavelength is in the range of about 450 to about 600 nm.
22. The use of a vaccine as defined in any one of claims 18 to 21 for prevention, protection or treatment of an immunological disorder, infection and/or a cancer.

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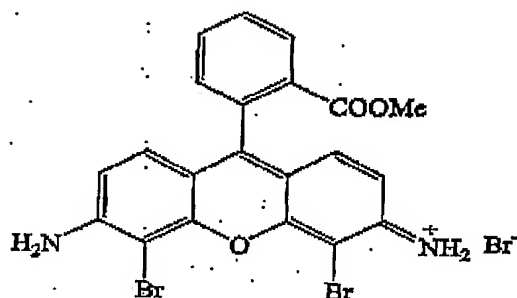
23. The use of claim 22, wherein said immunological disorder is an alloimmune disorder or an autoimmune disorder.
24. The use of claim 23, wherein said alloimmune disorder is Graft-versus-Host Disease or an organ rejection.
25. The use of claim 23, wherein said autoimmune disease is selected from the group consisting of Rheumatoid Arthritis, Multiple Sclerosis, Scleroderma, Lupus, Autoimmune Hemolytic Anemia, Diabetes Mellitus, Progressive Systemic Sclerosis, Idiopathic Thrombocytopenic Purpura, Psoriasis, Ulcerative Colitis and Crohn's Disease.
26. The use of any one of claims 22 to 25, wherein said infection is caused by a bacteria, a virus, a parasite, a fungus, a prion or a protozoan.
27. The use of claim 26, wherein said virus is selected from the group consisting of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), Human Herpes Virus Type I or II, and Varicella Zoster.
28. The use of any one of claims 22 to 27, wherein said infection causes Chagas' Disease.
29. The use of any one of claims 22 to 28, wherein said cancer is selected from the group consisting of solid tumors and hematologic tumors.
30. The use of claim 29, wherein said solid tumors are of breast cancer, lung cancer, gastrointestinal cancer, skin cancer or of genitourinary, neurological, head and neck or musculoskeletal origin.
31. The use of claim 29, wherein said hematologic tumors are lymphomas, leukemias, myelomas, myelodysplasias or plasma cell dyscrasias.
32. A method of preparing an immunologic medicament for prevention, protection or treatment of an immunological disorder, infection and/or a cancer in an individual, which comprises the steps of :

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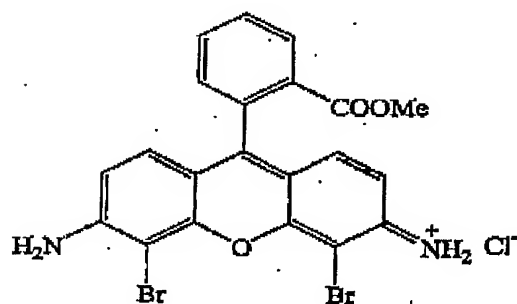
- 41 -

a) treatment of said cells with a photoactivatable molecule selected from the group consisting of:



I

4,5-dibromorhodamine 123 hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrobromide) also called TH9402,



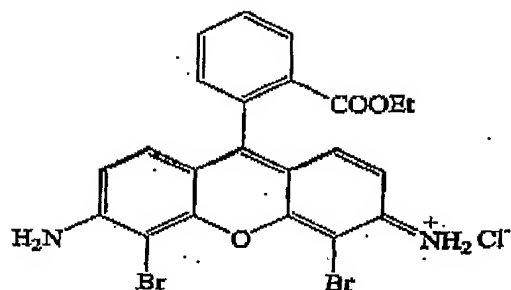
II

4,5-dibromorhodamine 123 hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride),

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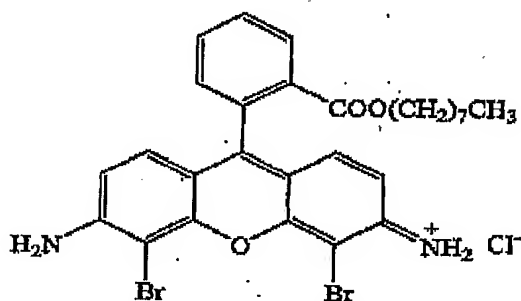
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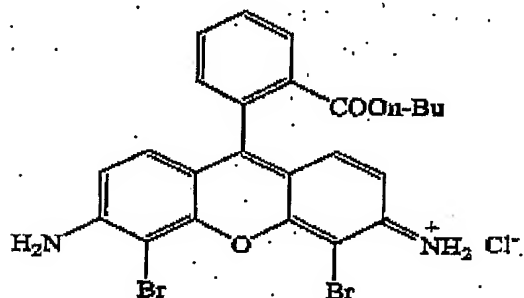
III

4,5-dibromorhodamine 110 ethyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrochloride),



IV

4,5-dibromorhodamine 110 octyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid octyl ester hydrochloride),

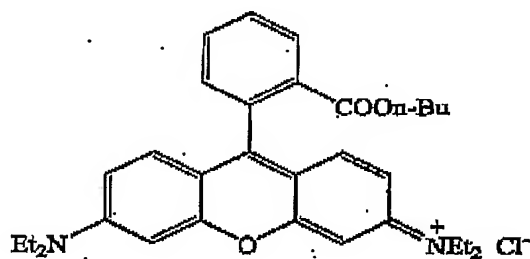


V

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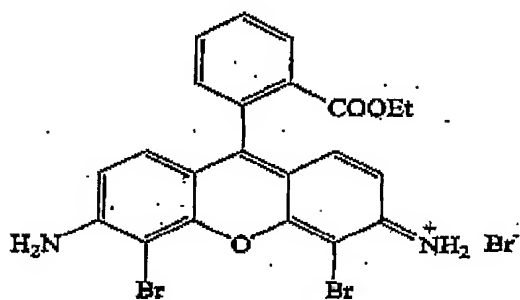
- 43 -

4,5-dibromorhodamine 110 n-butyl ester hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrochloride),



VI

rhodamine B n-butyl ester hydrochloride (2'-(6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrochloride),



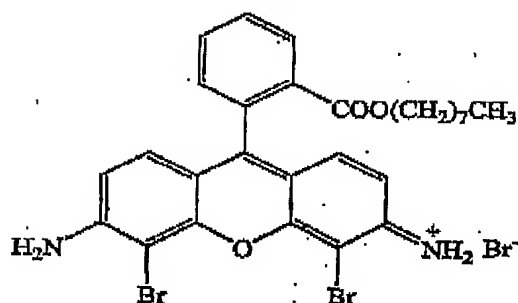
VII

4,5-dibromorhodamine 110 ethyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrobromide),

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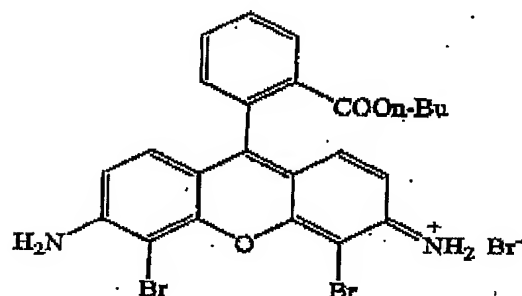
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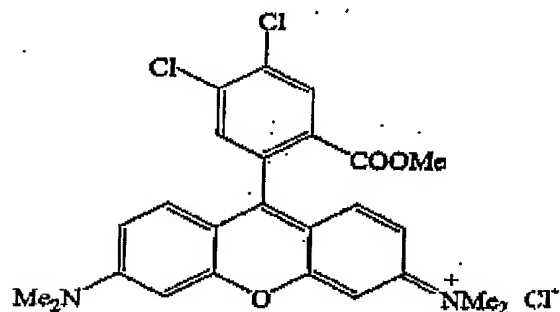
VIII

4,5-dibromorhodamine 110 octyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid octyl ester hydrobromide),



IX

4,5-dibromorhodamine 110 n-butyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)benzoic acid n-butyl ester hydrobromide),



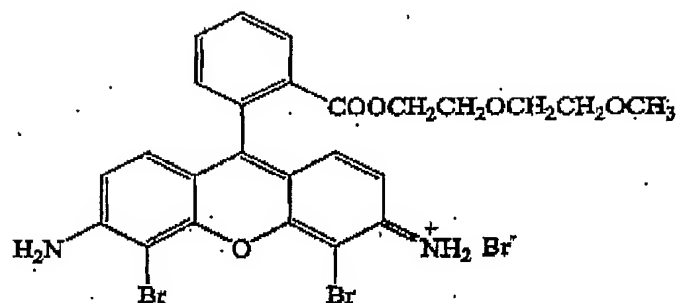
X

4',5'-dichlorotetramethylrhodamine (2'-(6-dimethylamino-3-dimethylimino-3H-xanthen-9-yl)-4',5'-dichloro benzoic acid methyl ester hydrochloride),

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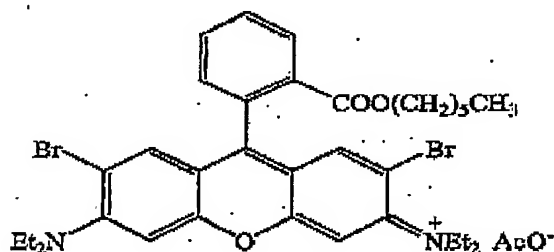
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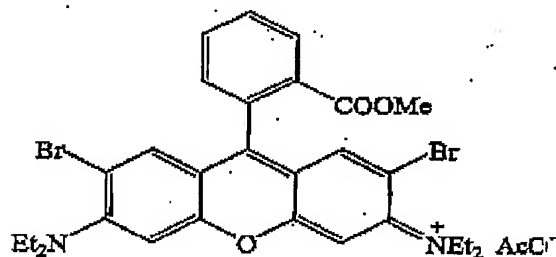
XI

4,5-dibromorhodamine 110 2-(2-methoxy ethoxy)ethyl ester hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid 2-(2-methoxy ethoxy) ethyl ester hydrobromide),



XII

2,7-dibromorhodamine B hexyl ester acetate (2'-(2,7-dibromo-6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid hexyl ester acetate),



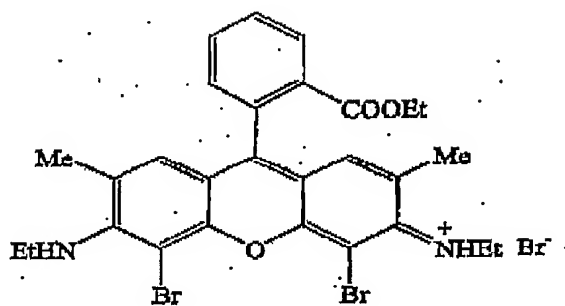
XIII

2,7-dibromorhodamine B methyl ester acetate (2'-(2,7-dibromo-6-diethyl amino-3-diethyl imino-3H-xanthen 9-yl)benzoic acid methyl ester acetate),

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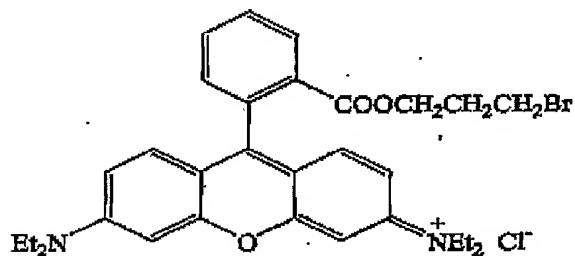
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XIV

4,5-dibromorhodamine 6G hydrobromide (2'-(4,5-dibromo-2,7-dimethyl-6-ethylamino-3-ethylimino-3H-xanthen-9-yl)benzoic acid ethyl ester hydrobromide),



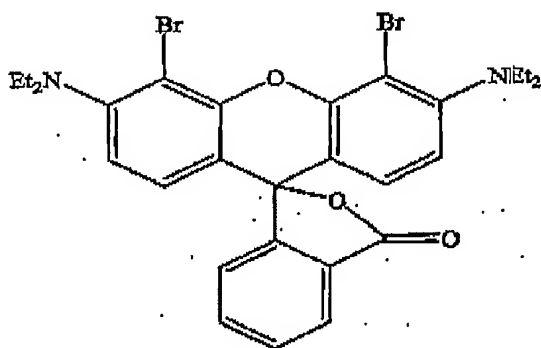
XV

rhodamine B 3-bromopropylester hydrochloride (2'-(6-diethyl amino-3-diethyl imino-3H-xanthen-9-yl)benzoic acid 3-bromopropyl ester hydrochloride),

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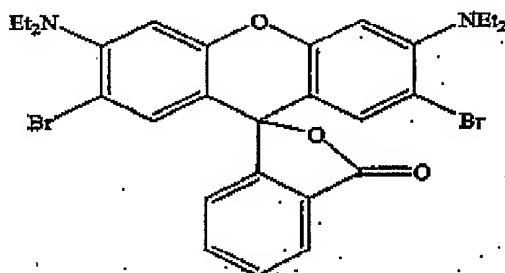
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XVI

4,5-dibromorhodamine B base (3,3-(4',5'-dibromo-3'-diethyl amino-6'-diethyl aminoxanthen-9'-yl)-3H-isobenzofuran-1-one),



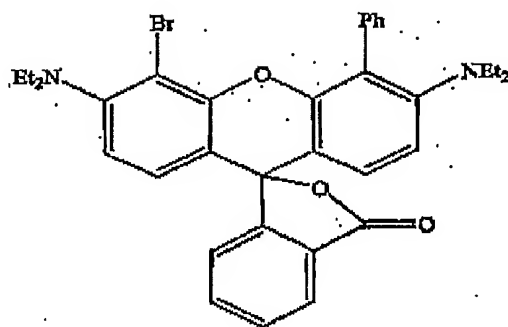
XVII

2,7-dibromorhodamine B base (3,3-(2',7'-dibromo-3'-diethyl amino-6'-diethyl aminoxanthen-9'-yl)-3H-isobenzofuran-1-one), and

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XVIII

4-bromo-7-phenyl-rhodamine B base (3,3-(4'-bromo-3'-diethyl amino-6'-diethyl amino-5'-phenyl xanthen-9'-yl)-3H-isobenzofuran-1-one).

and

b) subjecting said cells to a light of appropriate wavelength to activate said photoactivatable molecule, thereby obtaining PDT-treated cells (whole or fragments thereof) and/or supernatant thereof.

33. The method of claim 32, wherein said immunologic medicament is an autoimmune vaccine.

34. The method of claim 32 or 33, wherein said immunological disorder is an alloimmune disorder or an autoimmune disorder.

35. The method of claim 34, wherein said alloimmune disorder is Graft-versus-Host Disease or an organ rejection.

36. The method of claim 35, wherein said autoimmune disease is selected from the group consisting of Rheumatoid Arthritis, Multiple Sclerosis, Scleroderma, Lupus, Autoimmune Hemolytic Anemia, Diabetes Mellitus, Progressive Systemic Sclerosis, Idiopathic Thrombocytopenic Purpura, Psoriasis, Ulcerative Colitis and Crohn's Disease.

37. The method of any one of claims 32 to 36, wherein said infection is caused by a bacteria, a virus, a parasite, a fungus, a prion or a protozoan.

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38. The method of claim 37, wherein said virus is selected from the group consisting of Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), Human Herpes Virus Type I or II, and Varicella Zoster.

39. The method of any one of claims 32 to 38, wherein said infection causes Chagas' Disease.

40. The method of any one of claims 32 to 39, wherein said cancer is selected from the group consisting of solid tumors and hematologic tumors.

41. The method of claim 40, wherein said solid tumors are of breast cancer, lung cancer, gastrointestinal cancer, skin cancer or of genitourinary, neurological, head and neck or musculoskeletal origin.

42. The method of claim 40, wherein said hematologic tumors are lymphomas, leukemias, myelomas, myelodysplasias or plasma cell dyscrasias.

43. The method of any one of claims 32 to 42, wherein said treatment of said individual cells is effected *ex vivo* or *in vivo*.

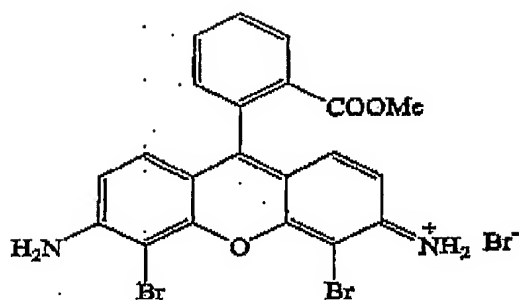
44. The method of claim 43, wherein said treatment is an *ex vivo* treatment effected by perfusion.

45. The method of any one of claims 32 to 44, wherein said photoactivatable molecule is selected from the group consisting of:

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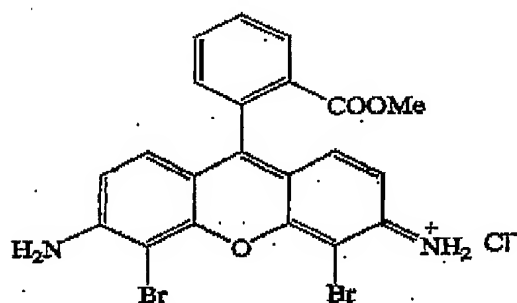
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I

4,5-dibromorhodamine 123 hydrobromide (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrobromide) also called TH9402, and



II

4,5-dibromorhodamine 123 hydrochloride (2'-(6-amino-4,5-dibromo-3-imino-3H-xanthen-9-yl)-benzoic acid methyl ester hydrochloride).

46. The method of any one of claims 32 to 45, wherein said wavelength is in the range of about 400 to about 800 nm.

47. The method of claim 46, wherein said wavelength is in the range of about 450 to about 600 nm.

48. The use of any one of claims 32 to 47, wherein step a) further comprises adding antigen presenting cells selected from the group consisting of dendritic cells, Langerhans cells and growth factors.

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OGILVY RENAULT

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49. The use of any one of claims 1 to 17, wherein said treatment is repeated.

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